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Reversed diastereoselectivity in the ring-opening reaction of (*S*)-TFPO with a chiral aminoacetonitrile Schiff base

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Abstract

Diastereoselective ring opening of (*S*)-2,3-epoxy-1,1,1-trifluoropropane [(*S*)-TFPO: 75% ee] with an aminoacetonitrile Schiff base bearing the (*R*,*R*,*R*)-hydroxypinanone chiral auxiliary [(*R*)-Schiff base] are described. The reaction of (*S*)-TFPO with the (*R*)-Schiff base selectively gave one diastereomer out of the four possible, while that with the (*S*)-Schiff base gave a complex mixture of all four possible diastereomers. The stereochemistry of the reaction products was greatly dependent on the base used for abstracting a proton from the (*R*)-Schiff base; utilization of LDA and KO^{t}Bu resulted in production of (*R*,*R*,*R*,*S*,*S*)- and (*R*,*R*,*R*,*R*,*S*)-isomers as the major diastereomers, respectively.

1. Introduction

The asymmetric alkylation of chiral Schiff base **1** prepared from glycinate and 2-hydroxy-3-pinanone is a versatile and efficient methodology for the synthesis of non-racemic chiral α-amino acids.[1,2] This successful methodology is characterized by its short and inexpensive procedure. Moreover, the absolute configuration of the products imino esters is easily predictable. Experimental[1,2] and theoretical[3] studies have demonstrated so far that (*S*)-imino esters were obtained from (1*R*,2*R*,5*R*)-2-hydroxy-3-pinanone, whereas the (1*S*,2*S*,5*S*)-enantiomer gave (*R*)-imino esters, in general (Scheme 1).

Though the reaction had been widely utilized for syntheses of optically active natural and non-natural amino acids, the electrophiles have been limited to halides. To our knowledge, there has been no example of the use of an epoxide as the electrophile with Schiff bases bearing the 2-hydroxy-3-pinanone moiety.[4] Two problems would arise from utilization of an epoxide as an

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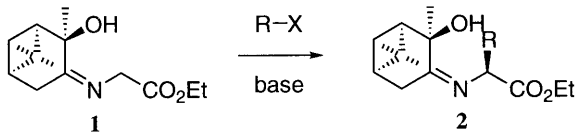
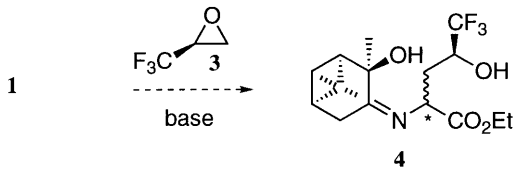


Scheme 1.

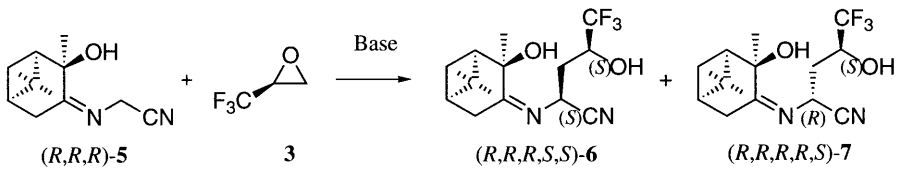
electrophile. One would be the problem of stereocontrol, since the reaction would be affected by both the chiral pinanone moiety and the chirality of an epoxide if present. The other would be the reactivity of an epoxide; an electron-withdrawing substituent such as a trifluoromethyl group on its epoxy ring would impact higher epoxide reactivity.

In our course of the development of the ring-opening reactions of (*S*)-2,3-epoxy-1,1,1-trifluoropropane **3** [(*S*)-TFPO; 75% ee] with carbon nucleophiles,[5] the above methodology was expected to be a suitable asymmetric variant for the synthesis of the chiral fluorinated amino acid,[6] 5,5,5-trifluoro-4-hydroxynorvaline (Scheme 2). Unfortunately, the ring-opening reaction of (*S*)-TFPO **3** with the chiral Schiff base **1** derived from ethyl glycinate gave only a trace of the product **4**. Indeed, this result is consistent with our previous results in which the ring-opening reaction of (*S*)-TFPO **3** with active methylene compounds required a cyano group as a substituent.[5]



Scheme 2.

Accordingly, we attempted to use the aminoacetonitrile Schiff base as a nucleophile precursor instead of glycinate **1**.[7] The ring-opening reaction of (*S*)-TFPO **3** with the ketenimine derived from aminoacetonitrile Schiff base **5** gave the expected ring-opening adducts **6** and **7** (Scheme 3). Interestingly, we encountered opposite diastereoselectivity for the reactions involving metal amide and alkoxide as bases.



Scheme 3.

We report here a new feature of the asymmetric alkylation of Schiff base **2** bearing the hydroxypinanone chiral auxiliary, in which both diastereomers (*R*,*R*,*R*,*S*,*S*)-**6** and (*R*,*R*,*R*,*R*,*S*)-**7** were selectively synthesized from the aminoacetonitrile Schiff base **5** bearing the (*R*,*R*,*R*)-hydroxypinanone chiral auxiliary by use of different bases.

2. Results and discussion

The starting aminoacetonitrile Schiff base **5**[7] was prepared from (*R*,*R*,*R*)-2-hydroxy-3-pinanone[1a] and aminoacetonitrile. Results for the ring-opening reaction of (*S*)-TFPO **3** with Schiff base **5** are summarized in Table 1. The configurations of the compounds **6** and **7** were confirmed by X-ray crystallographic analyses. The ORTEP diagrams of **6** and **7** are shown in Figs. 1 and 2, respectively.

Table 1
The ring-opening reaction of TFPO with aminoacetonitrile Schiff base (*R*,*R*,*R*)-**5**

Entry	Base (equiv.)	Additive (equiv.)[a]	(**6**+**7**): yield (%)[b]	Diastereomer ratio (**6**:**7**)[c]
1	LDA (2.0)	–	42	80:20
2	LTMP (2.0)	–	32	80:20
3	LDA (2.0)	$Cu(OTf)_2$ (0.1)	80	83:17
4	LDA (2.0)	$Sc(OTf)_3$ (0.1)	86	82:18
5	LDA (2.0)	$Yb(OTf)_3$ (0.1)	97	83:17
6	LDA (2.0)	$Yb(OTf)_3$ (0.5)	39	86:14
7	LDA (2.0)	$Yb(OTf)_3$ (1.0)	14	88:12
8	LiO^{t}Bu (2.0)	–	39	8:92
9	KO^{t}Bu (2.0)	–	73	9:91
10	KO^{t}Bu (2.0)	$Yb(OTf)_3$ (0.1)	68	8:92
11	LiHMDS (2.0)	$Yb(OTf)_3$ (0.1)	37	52:48
12	NaHMDS (2.0)	$Yb(OTf)_3$ (0.1)	49	47:53
13	KHMDS (2.0)	$Yb(OTf)_3$ (0.1)	46	22:78

[a] Additives were added immediately through the finger tube after the addition of TFPO.
[b] Isolated yields of diastereomer mixtures.
[c] Diastereomer ratios were determined by ^{19}F NMR.

Lithium amides such as LDA or LTMP gave the expected diastereomers **6** and **7** in moderate yields (entries 1 and 2). The addition of a catalytic amount of $Cu(OTf)_2$ dramatically enhanced the chemical yield to 80% (entry 3). Other metal triflates, such as $Sc(OTf)_3$ and $Yb(OTf)_3$, also enhanced the yield up to 86 and 97%, respectively (entries 4 and 5).[8] Addition of metal halides (LiCl, LiBr, $MgBr_2$, $ZnBr_2$, $TiCl_4$ and so on) as Lewis acids did not give the desired adducts **6** nor **7**, but halohydrins through halo-metallation of TFPO.[9] Interestingly, the use of LiO^{t}Bu as a base gave the ring-opening products **6** and **7** in 39% yield with the reversed diastereoselectivity (entry 8). The major diastereomer was (*R*,*R*,*R*,*R*,*S*)-**7**, the stereochemistry of which was determined by X-ray crystallographic analysis. Use of KO^{t}Bu instead of LiO^{t}Bu enhanced the chemical yield up to 73% (entry 9). These results imply that the first proton abstraction step is important for the diastereoselectivity of the reaction of Schiff base **5** with (*S*)-TFPO **3**, where Lewis acid catalysts did not enhance the chemical yield at all (entry 10).

We examined changing the metal ions for the ketenimine intermediates in the metal amide case. The reactions with LiHMDS, NaHMDS and KHMDS bases gave the products **6** and **7** with a slight change of diastereoselectivity from Li to K,[10] although it was not entirely clear because of their low chemical yields (entries 11–13).

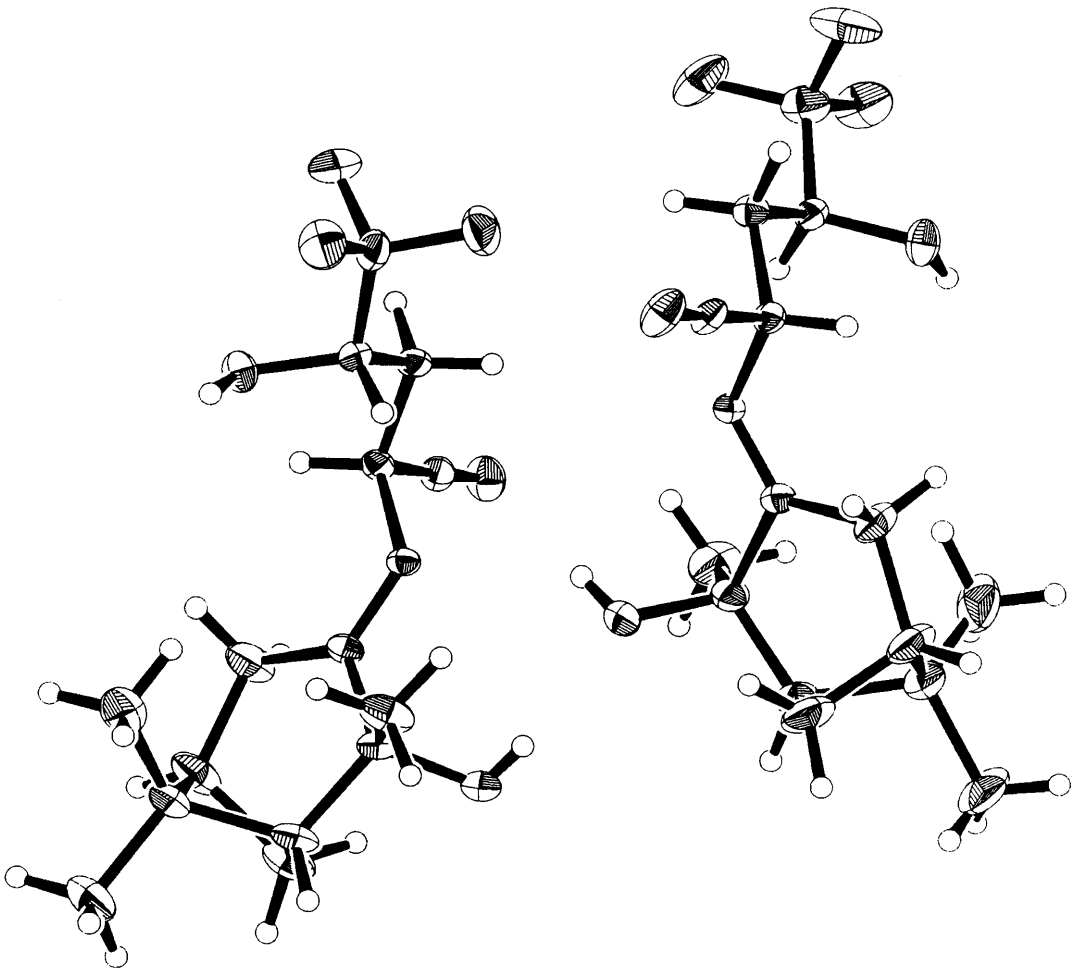


Figure 1. ORTEP diagram of (*R*,*R*,*R*,*S*,*S*)-**6**

We also examined the reaction of (*S*)-TFPO **3** with the (*S*,*S*,*S*)-aminoacetonitrile Schiff base **8** (Scheme 4). Surprisingly, we observed the lower chemical yield and lower diastereoselectivity, even under the same reaction conditions as in Table 1. The reaction with LDA/$Yb(OTf)_3$ and KO^{t}Bu gave the four diastereomers in 44 and 60% yields in the ratios of 7:48:23:22 (*S*,*S*,*S*,*R*,*R*:*unknown*:*unknown*:*S*,*S*,*S*,*S*,*R*) and 4:48:24:24, respectively. That is, the ratio of the compounds from (*S*)-TFPO:(*R*)-TFPO were 71:29 and 72:28, respectively, which is lower than the ratio (88:12) expected from the enantiomeric excess (75% ee) of the (*S*)-TFPO used.

These results presumably arise from mismatching of (*S*,*S*,*S*)-Schiff base **8** to (*S*)-TFPO **3**. Thus, the stereoselectivity should be kinetically controlled and not involve further diastereoselective protonation[11] of ketenimine derived from the product **5**. These results imply the possibility of using the present chiral Schiff base for the dynamic kinetic resolution of epoxides.[12]

The reversed stereoselectivity depends mainly on the conjugate anion of the base used, implying a possible contribution of lithiation of the hydroxyl group on the chiral hydroxy pinanone moiety to the stereochemistry of the products. The amide bases would convert the hydroxy group to the alkoxides[10] resulting in the major production of (*R*,*R*,*R*,*S*,*S*)-**6**, the

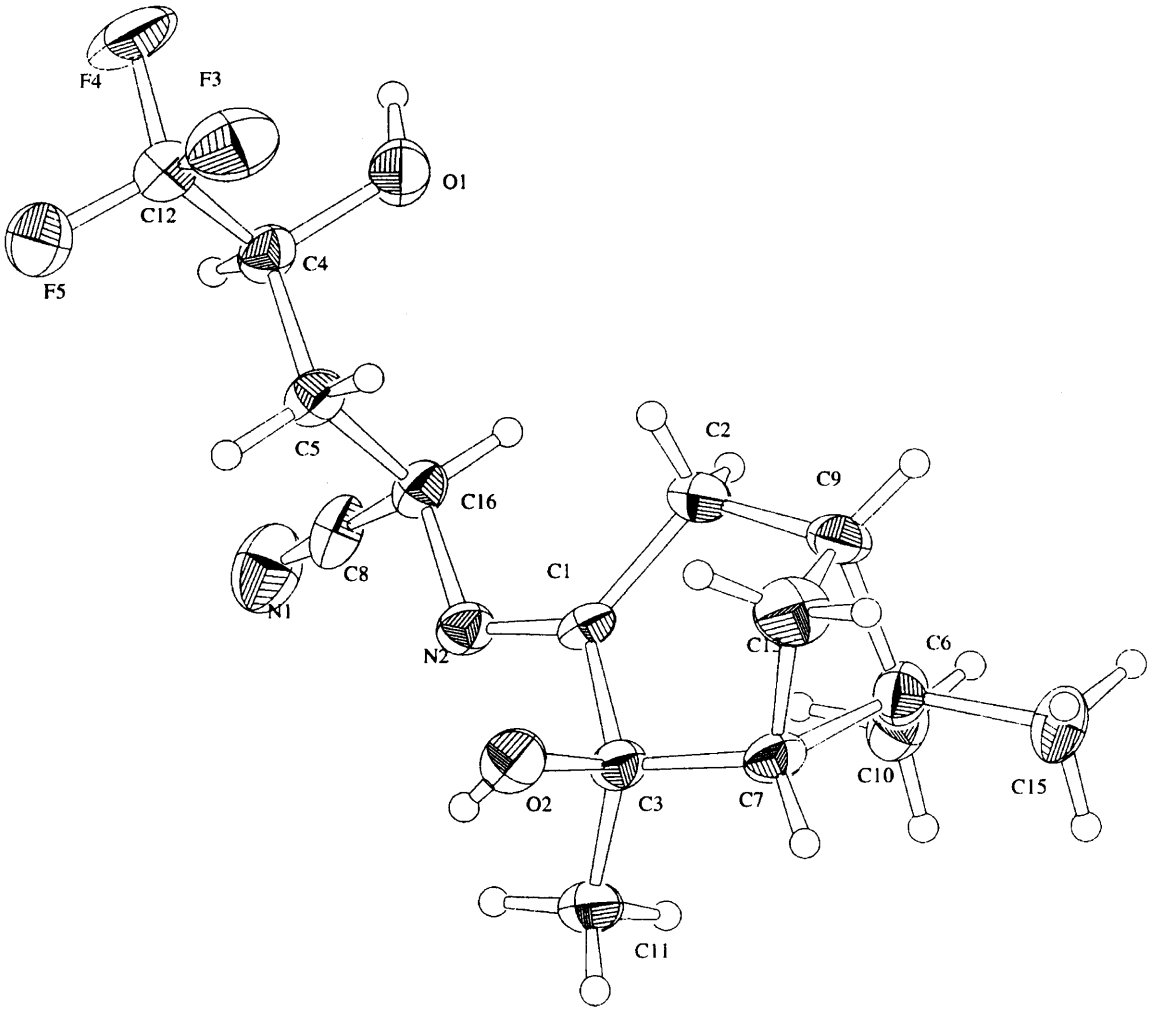
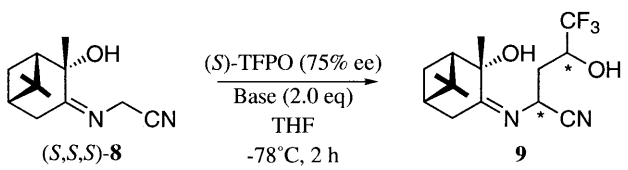


Figure 2. ORTEP diagram of (*R*,*R*,*R*,*R*,*S*)-**7**



Scheme 4.

stereochemistry is similar to the conventional alkylation of chiral Schiff base **1** by alkyl halides.[1] On the other hand, the alkoxide bases, which would not necessarily generate pinanone alkoxide,[10] resulted in the major production of (*R*,*R*,*R*,*R*,*S*)-**7**. The later case is similar to the Michael addition of chiral Schiff base **1** to vinyl phosphorus compounds,[2] which is the sole example of giving (*R*)-isomers from (*R*,*R*,*R*)-Schiff base **1**.

3. Conclusion

Two methods for controlling the diastereoselectivity have been presented for the stereoselective ring-opening reactions of chiral epoxides with chiral Schiff base **5**. The first is the matching or mismatching of the chiralities between the epoxide and the metallo-ketenimine with the chiral hydroxy pinanone moiety. Unfortunately, this possibility for dynamic kinetic resolution is presently not efficient enough to use racemic epoxides. The other is the base species that sometimes reverses the stereochemistry of the newly produced stereogenic center. The latter enables us to obtain both diastereomers of the aminonitriles from the chiral epoxides. Further studies on the scope of the reaction, the detailed mechanism, and conversion of the present products **6** and **7** to 5,5,5-trifluoro-4-hydroxynorvalines is now in progress.

4. Experimental

^{19}F (188 MHz), ^{1}H (200 MHz) and ^{13}C NMR (50 MHz) spectra were recorded on a Varian VXR-200 spectrometer (δ in ppm referred to C_6F_6 for ^{19}F NMR spectra and to TMS for ^{1}H and ^{13}C NMR spectra, J in Hz). Infrared spectra were recorded on a Hitachi Model 270-30 infrared spectrometer (ν in cm^{-1}). Melting points were determined on a Yanako MP-S3 melting point apparatus. Optical rotation was measured in a cell with 50 mm length and 1 mL capacity using a Horiba High Sensitive Polarimeter SEPA-300. A Perkin–Elmer series II CHNS/O Analyzer 2400 was employed for elemental analysis. X-Ray intensity measurements were carried out on a Rigaku RAXIS-IV imaging plate area detector.

*4.1. (2′*R,*3′*R,*5′*R,*2*S,*4*S)-2-[(2′-Hydroxypinylidene)amino]-5,5,5-trifluoro-4-hydroxypentanenitrile (*R,R,R,S,S)-*6*

To a mixture of aminoacetonitrile Schiff base **2** (1 mmol) and lithium diisopropylamide (LDA: 2 mmol; freshly prepared from 1.4 M MeLi in ether (2 mmol) and diisopropylamine (2 mmol)) in THF (3 mL) was added TFPO **3** (5 mmol) at −78°C under an Ar atmosphere, immediately followed by the addition of $Yb(OTf)_3$ (0.1 equiv.) through the finger tube apparatus. After 2 h, the reaction was quenched with aq. NH_4Cl. The reaction mixture was extracted with ether, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude products were purified by silica gel column chromatography (hexane:EtOAc = 3:1) to afford two diastereomeric isomers in 97% yield [(*R*,*R*,*R*,*S*,*S*)-**6**:(*R*,*R*,*R*,*R*,*S*)-**7** = 83:17 determined by ^{19}F NMR using 1,3-bis(trifluoromethyl)benzene as an internal standard] as a white solid. After purifying once again with silica gel column chromatography (hexane:EtOAc = 5:1), a sole diastereomer (*R*,*R*,*R*,*S*,*S*)-**6** was isolated in 45% as a white solid. Recrystallization from ether–hexane solution gave a diastereomer (*R*,*R*,*R*,*S*,*S*)-**6** as colorless needles. $[\alpha]_D^{28}$ −165.8 (*c* 0.240, $CHCl_3$). Mp 147–148°C. IR (KBr) 3410, 2260, 1650. ^{19}F NMR ($CDCl_3$) δ 82.3 (d, J = 7 Hz, 3F). ^{1}H NMR ($CDCl_3$) δ 0.81 (s, 3H), 1.36 (s, 3H), 1.48 (s, 3H), 1.64–1.69 (m, 2H), 2.10 (s, 1H), 2.12 (d, J = 6.4 Hz, 2H), 2.15–2.55 (m, 2H), 2.57–2.90 (m, 2H), 3.99 (d, J = 4.2 Hz, 1H), 4.32 (qdd, J = 6.8, 9.4, and 2.6 Hz, 1H), 4.68 (ddd, J = 8.2, 3.8, and 1.0 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 22.7, 27.0, 27.8, 28.0, 33.3, 34.1, 38.0, 38.5, 45.8, 50.3, 67.8 (q, J = 32 Hz), 76.5, 116.8, 124.6 (q, J = 280 Hz), 185.6. Anal. calcd for $C_{15}H_{21}F_3N_2O_2$: C, 56.60; H, 6.65; N, 8.80. Found: C, 56.78; H, 6.69; 8.89. Crystal data for **6**; $C_{15}H_{21}F_3N_2O_2$; Mr = 636.68 (for a pair of two

molecules 318.341×2); orthorhombic; $P2_12_12$ (#18); $a=18.110(3)$, $b=24.544(3)$, $c=7.6479(6)$ Å, $V=3399.3899$ Å^3, $Z=4$, $Dx=1.24$ g cm^{-3}; $\mu=1.04$ cm^{-1} for Mo Kα radiation ($\lambda=0.7107$ Å); observed at 150 K. The structure was solved by a direct method (SIR 92), and refined by a full-matrix least-squares method. Final R was 0.034 and Rw was 0.032 for 2515 reflections with $I_0>3.00\sigma$ (I_0). Reflection/parameter ratio was 5.73, goodness of fit indicator was 1.39. Max. shift/error in final cycle was 0.13.

4.2. (2′R,3′R,5′R,2R,4S)-2-[(2′-Hydroxypinylidene)amino]-5,5,5-trifluoro-4-hydroxypentanenitrile [(R,R,R,R,S)-7]

To a mixture of aminoacetonitrile Schiff base **2** (1 mmol) and potassium *tert*-butoxide (2 mmol) in THF (3 mL) was added TFPO (**3**: 5 mmol) at −78°C under Ar atmosphere. After 2 h, the reaction was quenched with aq. NH_4Cl. The reaction mixture was extracted with ether, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude products were purified by silica gel column chromatography (hexane:EtOAc=3:1) to give two diastereomeric isomers in 73% yield [(*R*,*R*,*R*,*S*,*S*)-**6**:(*R*,*R*,*R*,*R*,*S*)-**7**=9:91 determined by ^{19}F NMR using 1,3-bis(trifluoromethyl)benzene as an internal standard] as a white solid. Recrystallization from ether–hexane solution gave a sole diastereomer (*R*,*R*,*R*,*R*,*S*)-**7** as colorless needles (53%). $[\alpha]_D^{28}$ −124.8 (*c* 0.336, $CHCl_3$). Mp 155–157°C. IR (KBr) 3420, 3260, 2280, 1650. ^{19}F NMR ($CDCl_3$) δ 81.7 (d, $J=6$ Hz, 3F). ^{1}H NMR ($CDCl_3$) δ 0.88 (s, 3H), 1.35 (s, 3H), 1.51 (s, 3H), 1.51–1.57 (m, 2H), 2.10 (d, $J=5.4$ Hz, 1H), 2.24 (s, 1H), 2.26–2.48 (m, 2H), 2.52–2.88 (m, 2H), 3.57 (d, $J=4.2$ Hz, 1H), 4.20–4.42 (m, 1H), 4.54 (ddd, $J=6$, 8, and 1 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 20.8, 25.0, 25.9, 26.0, 31.9, 32.2, 36.1, 36.8, 44.6, 48.3, 66.1 (q, $J=32$ Hz), 74.9, 115.0, 122.4 (q, $J=280$ Hz), 182.2. Anal. calcd for $C_{15}H_{21}F_3N_2O_2$: C, 56.60; H, 6.65; N, 8.80. Found: C, 56.94; H, 6.58; N, 8.98. Crystal data for **7**; $C_{15}H_{21}F_3N_2O_2$; $Mr=318.34$; orthorhombic; $P2_12_12_1$ (#19); $a=7.4042(4)$, $b=8.9804(4)$, $c=25.063(1)$ Å, $V=1666.5(1)$ Å^3, $Z=4$, $Dx=1.27$ g/cm^3; $\mu=1.07$ cm^{-1} for Mo Kα radiation ($\lambda=0.7107$ Å); observed at rt. The structure was solved by a direct method (SIR 92), and refined by a full-matrix least-squares method. Final R was 0.059 and Rw was 0.072 for 1629 reflections with $I_0>3.00\sigma$ (I_0). Reflection/parameter ratio was 7.37, goodness of fit indicator was 3.61. Max. shift/error in final cycle was 0.09.

Acknowledgements

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